

Chronic Kidney Disease and Cognitive Impairment: The Kidney-Brain Axis

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Keywords

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Abstract

Background: Cognitive impairment, increasingly recognized as a major social burden, is commonly found in chronic kidney disease (CKD) patients. **Summary:** Vascular damage, uremic toxicity, oxidative stress, and peripheral/central inflammation induced by CKD might be involved in brain lesions and ultimately result in cognitive decline. Uncovering the pathophysiology of CKD-associated cognitive impairment is important for early diagnosis and prevention, which undoubtedly prompts innovative pharmacological treatments. **Key Messages:** Here, we sequentially review the current understanding and advances in the epidemiology, risk factors, and pathological mechanisms of cognitive impairment in CKD. Furthermore, we summarize the currently available therapeutic strategies for cognitive impairment in CKD.

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Introduction

Chronic kidney disease (CKD), also known as chronic kidney failure, is a gradual loss of kidney function that manifests in a decrease in the glomerular filtration rate or an increase in urinary albumin excretion. As an impor-

tant risk factor for morbidity, CKD is a major health burden world-widely. According to the 2019 Global Burden of Disease, 697.29 million people worldwide suffered from CKD, which caused about 1.427 million deaths. Global prevalence and incidence of CKD were shown to be 9.37% and 0.05%, respectively, in 2019 [1, 2]. CKD-related complications include kidney disease progression, acute kidney injury, anemia, mineral and bone disorders, increased all-cause and cardiovascular mortality, and especially cognitive impairment [3]. Cognitive impairment and deficits in one or more key brain functions, such as learning, memory, and sensory processing, have often been observed as accompanying symptoms of CKD, with a prevalence that depends on the stage of CKD among 16% and 38% [4]. At the end stage of renal disease, which requires hemodialysis, 85% of patients endure memory loss, difficulty in execution, or language deficits [5]. Cognitive impairment begins early in the course of the CKD and parallels kidney function decline [6]. A substantial number of patients with CKD suffer from cognitive dysfunction. Hence, CKD is deemed as one of the strongest risk factors for mild cognitive impairment and dementia. It is especially worth noting that CKD is closely related to Alzheimer's disease (AD), stroke, and cerebrovascular disease [7]. In fact, an 11-year follow-up study elucidated that albuminuria and microalbuminuria, as early markers of endothelial damage of the renal glomeruli, could help predict cognitive decline [8]. However, the intricate pathogenic relationship and exact

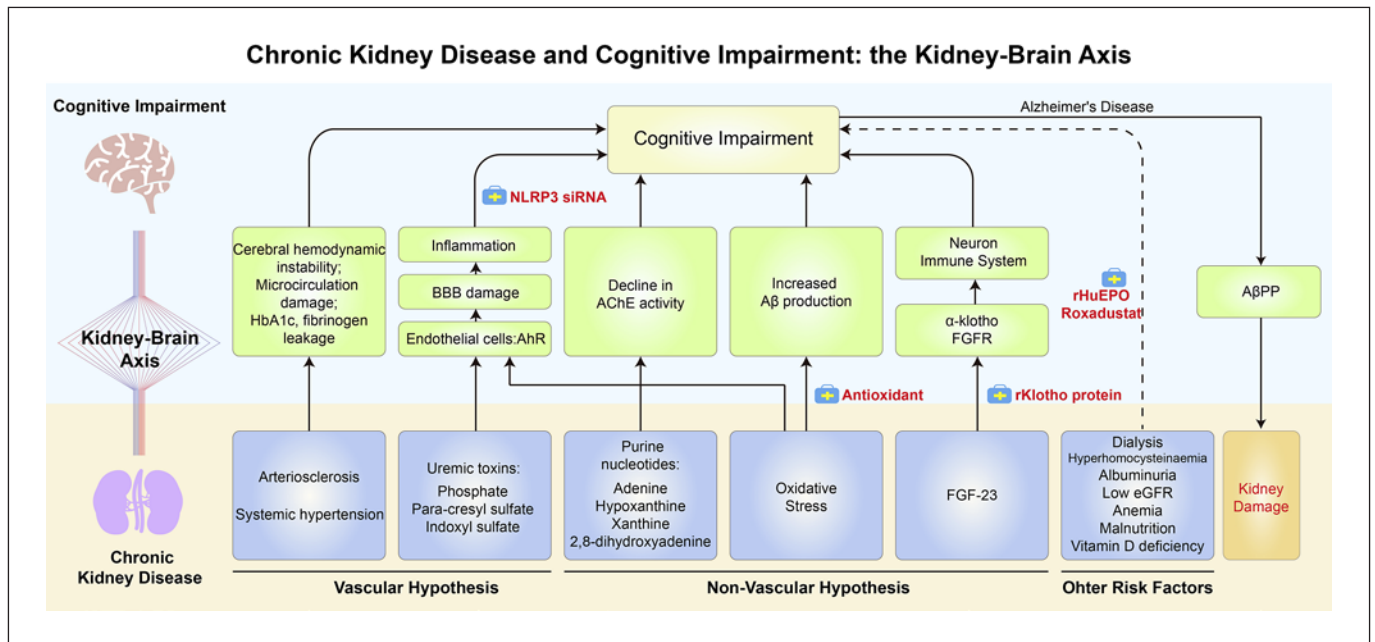


Fig. 1. Schematic representation of the potential mechanism of cognitive impairment in patients with CKD and treatment strategies. In CKD-induced cognitive impairment, vascular hypothesis includes systemic hypertension, arteriosclerosis, and uremic toxin-related pathways. The nonvascular hypothesis contains purine nucleotides, oxidative stress, and FGF23-related pathways. These hypotheses together with other known factors such as albuminuria or anemia contribute to cognitive impairment. Specifically, CKD-related vascular damage can contribute to cognitive impairment by inducing impaired cerebral hemodynamics, altered brain microcirculation, or leakage of hemoglobin (HbA1c) and fibrinogen from vessels. Accumulation of uremic toxins, including phosphate, IS, and PCS, is agonists of the transcription factor AhR in endothelial cells. Activation of AhR leads to BBB disruption and subsequently increases the transportation of inflammatory immune cells and proteins into the brain. Purine nucleotides alter the

activity of AChE which is associated with cognitive impairment. Oxidative stress leads to the cleavage of APP and Aβ production. Increased FGF23 directly impacts hippocampal neurons or interferes with the immune system. Therapies and interventions include inflammasome-targeted RNA interference approaches such as NLRP3 siRNA. The antioxidant drug 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl shows potential to improve cognitive dysfunction in the CKD model. Recombinant klotho proteins are used to treat and/or prevent CKD by reducing inflammation and injury. For risk factors such as anemia, rHuEPO is the standard therapy and also acts as a neuroprotective agent. Roxadustat (FG-4592) is a PHD inhibitor that can stimulate endogenous EPO production. These anti-anemia drugs exhibit beneficial effects on CKD-induced cognitive impairment. In the context of AD, neuron-specific expressed Aβ can cause BACE-mediated kidney damage. PHD, prolyl-hydroxylase domain.

modulation mechanisms between CKD and cognitive impairment remain unclear and require in-depth clarification. Understanding kidney-brain interplay is a multidisciplinary issue in the scientific field. These basic scientific findings will provide translational values for developing new therapeutic strategies to prevent, treat, or reverse CKD-related cognitive impairment.

Risk Factors Leading to Cognitive Impairment in CKD

Traditional risk factors for cognitive impairment in CKD include aging, female gender [9], education status, nonwhite ethnicity, diabetes mellitus [10], hypertension,

and cardiovascular disease, which have been extensively reviewed recently [7, 11–14]. Here, we will discuss the nontraditional risk factors in depth, including hyperhomocysteinemia, oxidative stress, low estimated glomerular filtration rate (eGFR), albuminuria, malnutrition, and inflammation (shown in Fig. 1).

Low eGFR and albuminuria are both independent risk factors for cognitive impairment. A study assessing the level of albuminuria demonstrated that urine albumin-creatinine ratio of 30–299 and ≥ 300 mg/g is associated, respectively, with 31% and 57% higher risk of cognitive impairment [15]. This study included a relatively large patient cohort with baseline standardized albuminuria measurements and a prospective assessment of cognitive

function using a validated measure. This finding supports the incorporation of albuminuria information into CKD classification methods.

Although dialysis differentially benefits CKD patients' life quality and alleviates uremic symptoms, such as depressive symptoms, pruritus, sleep disturbances, etc. [16], plenty of studies have shown that patients undergoing dialysis are more likely to have cognitive impairment [17]. A 676-patient study showed that 79.4% of hemodialysis patients progress to cognitive impairment [18]. A meta-analysis indicated people treated with hemodialysis have worse cognition than the general population, particularly in their attention (95% CI: -1.18 to -0.68) [19]. However, these meta-analysis studies had uncertain risk of bias. First, they were not fully adjusted for education. Second, a wide range of tests were used to assess cognition which might cause high heterogeneity. Furthermore, other data regarding differences between people who received hemodialysis and those who received peritoneal dialysis were insufficient.

Uremic toxins are accumulated due to the deterioration of the renal clearance function and cause many deleterious effects, such as systemic inflammation, cardiac failure, anemia, immune dysfunction, anorexia, neurological damage, and cognitive impairment. Uremic toxins produced in CKD can pass through the blood-brain barrier (BBB) and cause cognitive dysfunction and neurodegeneration. Uremic toxins such as phosphate, para-cresyl sulfate (PCS), indoxyl sulfate (IS), and fibroblast growth factor 23 (FGF23) have been reported to increase the risks of cognitive impairment in patients with CKD [20]. A study recruiting 199 patients with CKD and 84 control subjects revealed that the patients with higher serum PCS and IS levels had a poorer cognitive function in the early stage of CKD [21]. Besides, neuronal damage induced by uremic toxins may be more important than disturbed hemodynamic factors or lipid metabolism in cognitive impairment pathogenesis. Notably, experimental models showed that the brain monoaminergic system is susceptible to uremic neurotoxins [22].

Acetylcholinesterase (AChE) activity is closely associated with dementia and cognitive impairment. Purine nucleotides and uric acid, relevant to the increased prevalence and progression of CKD, have been found to alter the activity of AChE. Other CKD-associated metabolites, such as adenine, hypoxanthine, xanthine, and 2,8-dihydroxyadenine, also potentially play a role in inhibiting the activity of AChE [23].

Homocysteine, which has been verified detrimental to the brain, increases in the blood of CKD patients and therefore is related to worse cognitive and motor impair-

ment. The possible underlying mechanism is that homocysteine may contribute to the pathogenesis of neuronal damage by overstimulation of N-methyl-D-aspartate receptors resulting in excessive Ca^{2+} influx and reactive oxygen generation [24]. From this point, homocysteine may play a vital role in vascular dementia and AD [25].

Cystatin C, a protease inhibitor, is a measurement indicator of kidney function and a biomarker of cognitive impairment. A study found that a higher serum cystatin C level is associated with a greater likelihood of poor cognitive attention and executive function performance in individuals with CKD [26]. The results of this study are also consistent with longitudinal cohort studies of older adults that demonstrated an association between elevated cystatin C levels and incident-induced cognitive impairment [27, 28].

Anemia and malnutrition are commonly observed among patients with CKD, which may impair oxygen delivery to the brain, affect brain metabolism, and increase the prevalence and severity of cognitive impairment. Administration of erythropoietin (EPO) in CKD patients with anemia significantly improves cognitive function [29].

Vitamin D deficiency has been associated with multitudinous physiopathologic mechanisms, including muscle weakness, bone loss, cardiovascular diseases, oxidative stress, inflammation, immune suppression, and neurocognitive impairment [30]. Vitamin D exerts neuroprotective and regulatory roles in the central nervous system, and its deficiency is general in patients with CKD. Hypovitaminosis D was found to be linked with endothelial dysfunction in nondialysis CKD patients [31]. Therefore, endothelial function may be improved and the cardio-cerebrovascular events may be reduced by vitamin D supplementation in CKD patients [32].

Mechanisms of Cognitive Dysfunction in CKD

Several possible physiopathologic mechanisms are underlying the cognitive dysfunction in CKD, including vascular/nonvascular hypothesis and risk factor-related pathways. Factors related to any of these pathways have the potential to promote the development of cognitive impairment (shown in Fig. 1). Further inquiry into these mechanisms is warranted.

Vascular Damage

Brain microhemorrhages in CKD have been confirmed by preclinical studies and clinical imaging of the

brain in patients [33]. Unquestionably, brain microbleeds indicate the BBB breakdown, which has been demonstrated intensively in AD settings. Hence, CKD patients are at a greater risk of developing stroke and cognitive impairment. As end organs on parallel trajectories, the brain and kidney have similar anatomical and functional features of the vasculature system, giving them a unique susceptibility to vascular injury. In general, the risk of developing atherosclerosis, hypertension, atrial fibrillation, and diabetes are increased by CKD-related vascular risk factors. In particular, vascular risk factors, such as inflammation and oxidative stress, insult low-resistance vascular beds and endothelial structures, trigger vascular pathologic changes, ultimately induce minor artery diseases in the brain and kidney.

Vascular damage, impaired cerebral hemodynamics and altered extracellular milieu are among the most important proposed mechanisms involved in the cognitive dysfunction in CKD. Increased artery stiffness and microvascular damage in CKD patients are related to the damage of brain microcirculation [34], which is confirmed to be related to cognitive impairment [35]. In addition, a cross-sectional study that enrolled 151 CKD patients with cognitive impairment showed an interconnection between kidney function, central pressure pulsatility, large artery damage, and the damage of brain microcirculation [36]. CKD patients concomitant with the cerebral vascular disease showed higher global cerebral blood flow than control subjects [37], potentially affecting brain function and cognitive performance [38]. In the CKD animal model, widespread macrovascular and microvascular damage exists in the subcortical monoaminergic and cholinergic systems [13].

Hemoglobin A1c (HbA1c) and fibrinogen as vascular risk factors are investigated to be potential predictors of cognitive impairment. After blood vessel injury, HbA1c and fibrinogen leak out of vessels and participate in the pathological process of CKD. It is noteworthy that higher HbA1c and fibrinogen predispose CKD patients to have worse memory and executive function. In a prospective study of 119 CKD patients at stages 3–5 and 54 control patients of the same age without CKD, linear regression analysis showed HbA1c and fibrinogen can predict cognitive ability among patients with CKD [39]. The strength point of this study was that the control group of patients without CKD had a similar vascular risk profile. These observations are therefore very relevant in the clinical setting.

Uremic Toxicity

Uremic toxicity may play a vital role in the elevated risk of developing cognitive impairment found among patients with CKD. Accumulation of uremic toxins may cause BBB breakdown, neurotransmitter derangement, and drug pharmacokinetics disturbance. The BBB is important for keeping the central nervous system stable from the peripheral circulation. Endothelial dysfunction is commonly observed in CKD patients. Impaired endothelial function in the kidney manifests in impaired glomerular filtration and proteinuria leakage. The renal toxic effects of uremia, calcium-phosphate, and other metabolic disturbances circularly exaggerate inflammatory or oxidative response, which may directly or indirectly insult the brain vasculature and accelerate cognitive decline [40]. One study found that elevated urea alters the actin cytoskeleton and tight junction proteins in cultured endothelial cells and consequently breaks down the BBB [33]. Aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor widely expressed in endothelial cells, has been discovered to induce the expression of xenobiotic-metabolizing enzymes, inflammatory cytokines, and adhesion molecules. The uremic toxin IS, acting as an agonist of AhR, activates the endothelial cells [41] and leads to BBB disruption in animal CKD model with cognitive impairment [42]. Hence, uremic toxins have emerged as potent ligands of AhR and are associated with cognitive dysfunction in patients with CKD [43].

Besides, urea and other metabolic waste products diffuse into the gut lumen and induce changes in the microbiota, leading to the generation of proteolysis waste products, such as IS, PCS, indole-3-acetic acid, and so on. Recent studies have suggested that IS and indole-3-acetic acid derived from the gut microbiota may participate in the inflammatory signaling pathway in CKD patients [44]. Thus, “gut-derived uremic toxins” may induce vascular damage and play a crucial role in the pathogenesis of cognitive impairment in CKD. Accumulating evidence suggests that to reduce nephrotoxin production or accumulation and/or to induce the production of renal-protective metabolites through manipulation of the gut microbiota represents a potential therapeutic strategy to improve renal function. And experimental evidence from the use of prebiotics, probiotics, and symbiotics already showed promising results.

Peripheral/Central Inflammation

Inflammation, another detrimental factor for cognitive impairment, plays a non-negligible role in CKD-as-

sociated cognitive decline. The circulating levels of specific inflammatory cytokines and immune cells have been found to change significantly in CKD patients.

The cytokines most frequently associated with the pathogenesis of CKD are IL-1 β , IL-6, TNF, transforming growth factor- β (TGF- β), and so on, which have been demonstrated to be involved in the process of cognitive dysfunction. IL-1 β has been reported to participate in aging processes and cognitive impairment in multiple brain domains. Correlation between high IL-6 levels and poor executive function and degeneration of GABAergic interneurons were also identified [45, 46]. It was shown that elevated levels of TNF- α derived from CX3CR1⁺ monocytes could modulate learning and learning-dependent dendritic spine remodeling, consequently inducing cognitive dysfunction [47]. Importantly, inhibition of TNF- α showed potential to improve cognitive performance [48]. TGF- β is a crucial regulator of cell survival and differentiation, BBB integrity, memory formation, and neuronal plasticity [49]. In CKD, TGF- β can induce renal fibrosis via Smads and other signaling pathways [50]. However, it remains to be fully explored whether certain inflammatory cytokines are the cause of the cognitive and behavioral changes associated with CKD. The role of the immune system in CKD-related brain dysfunction is needed to be further elucidated.

Changes in cytokines and other biomolecules affect immune cell differentiation, activation, and function. The immune equilibrium plays an important role in CKD-related cognitive decline by maintaining the body's tolerance and homeostasis. The main types of immune cells associated with the development and progression of CKD are macrophages and Th2 cells [51]. Of note, anti-inflammatory macrophages are related to the incidence of kidney fibrosis [52]. In a unilateral ureteral obstruction-induced kidney fibrosis model, Th2 cells were proved to play pivotal promoting roles [53]. Besides, Treg cells play a critical role in maintaining immune equilibrium by secreting anti-inflammatory cytokines, including IL-10, IL35, TGF- β , and so on. A study enrolling 71 patients with CKD elucidated that peripheral blood Treg and Th17 cell frequencies are lower in the group with cognitive impairment compared to those without cognitive impairment [54], indicating that peripheral blood Treg/Th17 cells are associated with cognitive impairment in CKD patients. However, the underlying mechanisms such as how these immune cells contribute to the maintenance of immune equilibrium, which specific cytokine is involved in the downstream of immune reaction, what kind of pathways are regulated remain unclear.

Oxidative Stress

Oxidative stress has been demonstrated as an important factor in aging-related neurodegenerative diseases, including AD. The connection between oxidative stress and cognitive dysfunction has been extensively investigated. Along with aging, reactive oxygen species (ROS) production increases and antioxidant function reduces, directly affecting synaptic activity and neurotransmission, leading to cognitive dysfunction [55]. Mechanistically, overloaded oxidative stress leads to cause cleavage of APP and A β production which are important pathophysiological characteristics of cognitive dysfunction. As an important risk factor in cognitive dysfunction, oxidative stress is also prevalent in CKD. As a metabolic organ, the kidney is rich in oxidation reactions in mitochondria, making it vulnerable to oxidative stress-induced damage. Several groups have shown that oxidative stress-associated inflammation and anemia can accelerate kidney disease progression. Elevated plasma oxidative stress and A β have been observed in CKD patients, which undoubtedly contribute to pathological changes within the brain and accelerate cognitive dysfunction [56]. Potentially, using the plasma oxidative stress and A β levels, a diagnostic method for the identification and confirmation of cognitive decline in CKD patients can be established.

FGF23/Alpha Klotho Axis

CKD is well characterized by the increased FGF23 and the deficiency of klotho, which is the co-receptor of FGF23. FGF23, produced in bones, plays an important role in mineral homeostasis. The co-receptor membrane alpha klotho (α -klotho) is expressed in the kidney and mediates a specific FGF23 signal pathway. The extracellular domain of transmembrane α -klotho can be cleaved by proteases and released into the circulation as soluble α -klotho. Recent findings suggest that FGF23 directly affects hippocampal neurons and may consequently impair memory and learning function in CKD patients [57]. Moreover, it was reported that FGF23 has direct effects on leukocytes and macrophages, mediating various immune responses [58]. In summary, an in-depth understanding of the molecular mechanisms of the FGF23/ α -klotho axis is significant for uncovering the cognitive decline and allows us to find new therapeutic strategies in CKD patients.

Impact of Cognitive Impairment on Kidney Function in AD

Although the molecular interaction between the kidney and brain is a recent research front in the scientific field, in traditional Chinese medicine, the kidney was believed to play an important role in maintaining the function of the brain [59]. AD is the most common neurodegenerative disease that is characterized by cognitive deterioration and memory loss. Like CKD, multiple risk factors, including hypertension, atherosclerosis, and diabetes mellitus, are also associated with AD. Shared pathophysiology may lead to cognitive decline in the progression of both CKD and AD.

Emerging evidence suggests that the renin-angiotensin system (RAS) may play roles in AD and CKD. Both peripheral and central RAS function alterations contribute significantly to cardiovascular homeostasis [60]. Clinical investigations suggested the association between angiotensin II type 1 receptor blockade and improved cognitive function and demonstrated an increased angiotensin II type 1 receptor expression in the postmortem cortex of AD patients in comparison with control patients [61]. Antihypertensive drugs including angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) decrease the risk of AD [62]. The use of ARBs such as losartan correlates with reduced onset and progression of AD. One study found that losartan could improve the cognitive performance in a mouse model of AD [63]. Besides, uremic toxin IS was proved to enhance leukocyte-endothelial interactions through upregulation of E-selectin [64], which is notable in AD development. CKD and AD are both characterized by the decrease of FGF23 co-receptor klotho. Recently, upregulation of klotho was shown to be a neuroprotective factor [65]. As discussed in Risk Factors Leading to Cognitive Impairment in CKD, kidney injury can contribute to impaired EPO secretion. In CKD, tubular-interstitial fibrosis leads to the loss of EPO secretion [66], while EPO was found to have the function to prevent A β accumulation by alleviating lipid peroxidation in animal experiments [67]. Therefore, EPO supplements may improve cognition in AD. Regarding the vitamin D deficiency in CKD, it was found that higher levels of active vitamin D were associated with better cognitive performance in AD patients. A 7-year follow-up indicated higher vitamin D dietary intake lowers the risk of developing AD among older women [68].

Interestingly, in an APP23 AD transgenic model, it was found that the increased APP protein can promote BACE1 expression in the kidney which contributes the

kidney damage [69]. This highlights a possible bidirectional communication between brain and kidney in the context of AD. In the present review, we provided an overview of the factors potentially involved in kidney-brain crosstalk. In our unpublished data generated from a cross-sectional AD patient cohort, we found that kidney injury-related metabolites such as creatinine and sarcosine are elevated in the plasma of AD patients. Despite the emerging evidence, significant advances in both clinical and experimental settings are needed to strengthen the conclusions.

Therapies and Interventions for Cognitive Impairment in CKD

Understanding the currently applied prevention and management strategies for CKD is critical for the treatment of CKD-related cognitive impairment [70]. Besides, as discussed in Mechanisms of Cognitive Dysfunction in CKD, several mechanisms were proposed to connect CKD with cognitive impairment. Therefore, interventions targeting those mechanisms also hold great promise. The following section will discuss these strategies which could potentially reduce the burden of dementia in CKD patients (shown in Fig. 1).

Anti-Anemia Drugs

Recombinant human EPO (rHuEPO), as standard therapy for CKD-associated anemia, has shown a neuroprotective effect. In a study evaluating the impact of rHuEPO on kidney damage and anemia in rats with CKD, treatment with rHuEPO not only improves the anemia but also significantly decreases the expression of BACE1, presenilin 1, A β , and lipid peroxidation, along with improved neuropsychological test scoring and sensorimotor and cognitive functions [71]. Therefore, rHuEPO can be considered as an effective neuroprotective agent in the context of CKD-associated cognitive dysfunction [72].

The inhibitors of the prolyl-hydroxylase domain, classical oral drugs for anemia, work by activating the hypoxia-inducible factors and stimulating the production of endogenous EPO. AstraZeneca recently published the data of roxadustat (FG-4592) from a phase III clinical trial which showed that the average hemoglobin levels and baseline changes from 28 to 52 weeks are a statistically significant improvement in dialysis-dependent CKD patients with anemia who received roxadustat and EPO alfa (epoetin alfa) combination therapy [73]. On August 19, 2021, the European Commission has approved the

Evrenzo™ (roxadustat) for the treatment of anemia symptoms in adult CKD patients [74]. Interestingly, one study showed that roxadustat could play an important role in promoting hippocampal neurogenesis and synaptic plasticity in rats [75]. As such, roxadustat may be used to treat anemia and improve the cognitive impairment in CKD patients.

Inhibitors of the RAS

RAS plays an important role in the pathogenesis of CKD. Notably, uremic toxins, such as IS, might induce the production of RAS metabolites in the CNS. As a result, the overload of angiotensin II in the brain might cause oxidative stress leading to cognitive dysfunction [53]. Additionally, nephrectomy accelerates cognitive impairment in AD mice through angiotensin II. Several studies have suggested that treatment with ARBs is associated with a lower risk of cognitive decline in dementia or AD [76, 77]. The amelioration of CKD-induced cognitive impairment in 5XFAD mice by ARB olmesartan appears to be mediated by the suppression of BBB disruption or oxidative stress [78]. Furthermore, treatment with angiotensin II receptor blocker telmisartan was shown to prevent spatial memory impairment by decreasing brain oxidative DNA damage and lipid peroxidation and improve cognitive impairment in the CKD mouse model [79], reinforcing the hypothesis that brain RAS is activated in CKD and possibly contributes to the associated cognitive decline [79]. Importantly, the application of ACEI captopril in the nephrectomy rat model suppressed the tyrosine nitration production, oxidative stress, and ROS-NO interaction in the cerebral cortex [80]. In general, the classical treatment strategy aiming to control the vascular risk factors such as ACE or ARB can improve cognitive function.

Anti-Inflammatory Agents

Inflammation is known to be associated with CKD progression. Recent studies have found that peripheral inflammation can significantly contribute to the central inflammation in different disease settings. In our previous finding, we found that gut microbiota-mediated peripheral inflammation can induce central inflammation in AD transgenic mice [81]. Therefore, inhibition of CKD-related peripheral inflammation to prevent cognitive impairment attracts much attention in the field. For example, increased uric acid could modulate NLR pyrin domain-containing protein 3 (NLRP3)/IL-1 β -related pathways by ROS activation and K⁺ efflux and consequently cause vascular endothelial cell damage, which is closely related to

microinflammation, oxidative stress, and disorders of lipid metabolism in the early stages of CKD. As such, an inflammasome-targeted RNA interference approach treats kidney injury and disease. In mice with 5/6 nephrectomy, knockout of NLRP3 can maintain better mitochondrial morphology and higher mitochondrial DNA copy number, indicating amelioration of mitochondrial abnormality [82]. NLRP3 siRNA reduces the expression of NLRP3 in subjects diagnosed with CKD and/or renal injury [83]. However, there are still no direct results demonstrating the cognition benefit from NLRP3 silence.

Anti-Diabetic Drugs

Type 2 diabetes mellitus (T2DM) is the main cause of CKD. In this population, the application of sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) was shown to be correlated with the decreased risk of cardiovascular and renal events. GLP-1 RAs, a new class of anti-hyperglycemic drugs, are demonstrated to improve cardiovascular and renal events in diabetic kidney disease patients and show cognitive-enhancing effects in animals [84].

Accumulated evidence in the past few years suggests that SGLT-2 inhibitors present potent neuroprotective properties. In clinical trials of patients with T2DM, these agents were shown to reduce albuminuria and proteinuria by 30–50% and the incidence of composite hard renal outcomes by 40–50% [85]. Meanwhile, SGLT2 inhibitors are detected in the central nervous system of aforesaid clinical subjects and possibly have neuroprotective properties. As expected, SGLT2 inhibition by empagliflozin has been shown to reduce amyloid burden in cortical regions of APP/PS1xd/db mice. Empagliflozin has a beneficial effect on cognitive function, which may be connected to an increase in cerebral brain-derived neurotrophic factors. Other SGLT2 inhibitors such as canagliflozin and dapagliflozin were shown to have AChE-inhibiting activity [86], which can be connected to the neuroprotective function.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are safe and well tolerated in T2DM patients with CKD and may reduce major risk factors for diabetic nephropathies, such as hyperglycemia and albuminuria [87]. Preclinical and clinical studies suggest that DPP-4 inhibitors may exert significant pleiotropic effects on CKD. Linagliptin, a DPP-4 inhibitor prescribed for T2DM patients who have CKD up to stage 3 and/or have eGFR (mL/min/1.73 m²) levels down to 45 or down to 30, shows beneficial effects in protecting against occurrence or progression of cognitive decline and/or reducing the risk of cognitive impair-

ment or dementia [88]. Since renal failure and T2DM are often comorbidities, the pharmacokinetics of T2DM agents may be affected, potentially increasing drug exposure and risk of adverse events.

Anti-Vascular Calcification Agents

Vascular calcification, another pathological feature in CKD, can induce renal dysfunction through high phosphate in mouse models of CKD with 5/6 nephrectomy. HMGB-1, a nuclear DNA-binding protein involved in inflammation, was recently identified as a proinflammatory mediator of tissue injury [89]. A cross-sectional study revealed that HMGB-1 is elevated significantly in CKD patients and correlates with glomerular filtration rate [90]. Another study suggested that HMGB1 is involved in vascular calcification associated with CKD via a mechanism involving the β -catenin [91]. Noteworthy, HMGB1 antagonists such as K883 have been tested in the preclinical treatment study of CKD and neurodegenerative diseases [92], which may serve as a promising treatment option. Further clinical studies, in placebo-controlled and double-blind way, are needed to elucidate the functional role of HMGB1 in CKD.

Others

Klotho, as an anti-aging protein mainly expressed in the kidney, is significantly associated with CKD development and progression. The deficiency of klotho results in white matter hyperintensities, microbleeds, microinfarctions, and cerebral atrophy through chronic inflammation, endothelial dysfunction, and vascular calcifications. Hence, changes in klotho levels may play a role in the development of cognitive impairment in CKD patients. Obviously, recombinant klotho proteins might be a hopeful treatment or prevention for CKD and associated cognitive impairment in the near future [93]. Importantly, given the critical role of oxidative stress in CKD-induced cognitive impairment, the anti-oxidative agents hold great promise for the treatment. One study showed that treatment with the antioxidant 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl significantly improved cognitive dysfunction in uremic mice [94]. A very recent study reported an increase of urine flow in APOE4-knock-in mice with bumetanide improved cognitive impairment. This finding in the animal model was consistent with the observation that patients using bumetanide had low AD risk [95]. Several proofs of principle strategies were proposed based on these findings for the management of CKD-related cognitive impairment. However, their clinical application will need to be assessed in the future.

Conclusion

Clinical characteristics of CKD patients include white matter injury, cerebral microbleeds, vascular dysfunction, and endothelial function, which are also shared by neurodegenerative diseases, including AD. From the holistic perspective, it is critical to consider the effects of distant tissue, such as kidneys, on the function of the brain and seek to understand the complex pathophysiological link between the brain and kidney in the future. In this review, we first discussed from the perspective of vascular injury. Due to the brain and the kidneys having many common anatomic and vasoregulatory features, CKD patients have cerebral hemodynamic change, which is likely to be the leading cause of cognitive impairment. In addition to cerebrovascular causes, other potential mechanisms, such as endothelial toxicity of the uremic state, could also be involved in cognitive impairment in CKD patients. Besides, we also discussed mechanisms linking to purine nucleotides, oxidative stress, and FGF23, which are still in the early stage and need to be further characterized in the future. The current treatment options for CDK aim at common risk factors, including ACEIs and ARBs, SGLT-2 inhibitors, GLP-1 RAs, and DPP-4 inhibitors. Other interventions such as compensatory EPO and the reduction of inflammation and oxidative stress may help ameliorate patients' clinical symptoms. In conclusion, the kidney and the brain interact in a strong and complicated way, often leading to the abnormal cognitive function for patients with CKD. Therefore, understanding the pathophysiologic interactions between brain function and kidney impairment is important for developing new therapies for the management of cognitive impairment in CDK patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Zuoquan Xie, Siyu Tong, Xingkun Chu, and Teng Feng drafted the manuscript. Meiyu Geng revised and approved the final manuscript.

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